
CORRESPONDENCE

Effectiveness of Adjuvant Fluorouracil in Elderly Colon Cancer Patients: The Internal and External Validity of Nonrandomized Research Design

To the Editor: The effectiveness of several therapeutic interventions in clinical practice, although suggested by well-conducted randomized controlled trials (RCTs) and systematic reviews and meta-analyses, is often taken as granted but it is seldom demonstrated. This is particularly true for the case of most chemotherapy regimens, as RCTs are carried out in selected samples, rarely reflecting the real-world setting. It has well documented, for example, that patients 65 years of age or older are underrepresented in cancer-treatment trials.¹ In addition, most of the new anticancer drugs (or new combinations of old drugs) seem to offer limited advantages over existing preparations, at least in terms of survival,² thus introducing the question whether the general population of cancer patients not involved in clinical trials would gain from the small benefit documented in the RCTs. Such an issue has become more relevant, as the current Food and Drug Administration (FDA) and European Medicinal Evaluation Agency (EMA) attitude to anticipate an earlier than ideal point along the drug approval path may lead to the marketing of drugs that are not effective or that are not safe.

For these reasons, the article by Iwashyna and Lamont³ is welcomed, as it gives empirical evidence about the effectiveness of adjuvant fluorouracil (FU)-based regimens in elderly patients with stage III colon cancer. The value of the article also relies on the fact that it is the result of well-applied statistical techniques on population-based cohort data from administrative databases, thus ensuring the external validity of the findings produced. Similar exercises were recently published by others for non-small-cell lung cancer and coronary artery disease^{4,5} and are to be interpreted in the context of the controversial issue of the value of observational studies for assessment of treatment effect.⁶ As a matter of fact, authors have applied state-of-the-art of methods now available to take into account, by design or by statistical adjustment, the selection bias introduced by the observational nature of the data. Nonetheless, a few points pertaining both the internal and external validity may be raised.

Briefly, the authors produced a propensity score for FU treatment using multivariable logistic regression analysis: A full, nonparsimonious model with 67 preselected variables was developed to produce the probability that a patient would be receiving the drug, and then such probabilities were used to perform a matched analysis to estimate the effect on survival. The "internal" validity of the approach was supported by the value of the *c* statistic that describes the discrimination of the model (0.83) and by sensitivity analyses that confirmed the robustness of results when a few relevant variables, such as comorbidity, were intentionally omitted by the predictive models (with a change of the hazard ratio from 0.73 to 0.59).

Both figures, the *c* value and the change in the estimated effect of FU after excluding comorbidity, indicate a particular caution in the interpretation of the findings. First, as there is not single universally accepted measure of the performance of a model, usually several statistics are estimated and reported, with the *c* statistic being only one of those recommended. A reader would be more confident about the results' validity if indicators of concordance and discordance (such as the Somers' D) and other summary statistics such as the *R*²-type and the goodness-of-fit measures were also given.⁷ It is unlikely that a model with 67 variables produces a *c* statistic much lower than that one reported by the authors. Second, a 20% change in the estimated benefit of FU when omitting just one variable, although important in such a population for its direct and indirect effect on survival, indicates that the model is not immune to the action of confounders or that bias is not taken into account in their analysis. The magnitude of the effect of removing comorbidity is compatible with the magnitude of the confidence intervals of the hazard ratio estimated by the full model.

As to the external validity of the findings, it should be mentioned that the generalizability of results is assured only for the United States context, as the propensity approach is based on the hypothesis that it balances only for the covariates that were used to construct the score.⁸ This means that, for example, present results cannot be applied to the European context, where other determinants are probably involved in the physicians' and patients' discussions of whether to use or not to use adjuvant FU after curative surgery.

Finally, in the discussion, the authors report that, "results suggest that adjuvant 5-FU would have benefited those untreated patients in the sample." We think that this statement, which has important implications for community physicians, should be more supported by data and findings, as what shown is not enough to support such a conclusion. To be able to agree with the authors' point of view on this particular aspect, we would need to know the comparison of survival (ie, the hazard ratio) across the strata based on the propensity to receive chemotherapy, from the lowest to the highest probabilities to receive chemotherapy. An example of such a way to evaluate the potential effectiveness of the treatment within strata of patients who are similar in terms of covariates is present in the literature.⁴ Only the stratification of patients based on their propensity to receive chemotherapy will show whether patients with less propensity for treatment appear to realize the same benefits as those with greater propensity.

In conclusion, this study has added further evidence about the value of outcome research in oncology but has also given another example of the dependence of observational approaches on statistics.

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In Reply: Apolone et al¹ raise important issues regarding the internal and external validity of our observational study² of the effects adjuvant fluorouracil (FU) in elderly Medicare beneficiaries with stage III colon cancer, and we thank them for their close reading of our paper.

With respect to internal validity, we agree that even rigorous statistical techniques cannot overcome all the limitations of observational data, and we made every effort to highlight those limitations in our article. Clearly, a superior solution to the problem of limited information on the benefits and toxicities of chemotherapy in elderly cancer patients is to increase their participation in clinical trials. Several cooperative oncology groups have sponsored chemotherapy trials of elderly cancer patients, for which exclusionary requirements include age less than 65 years. For example, the Cancer and Leukemia Group B is currently accruing patients to a randomized, controlled, adjuvant chemotherapy trial for women 65 years of age and older with breast cancer, examining the utility of standard adjuvant regimens (ie, doxorubicin and cyclophosphamide, or cyclophosphamide, methotrexate, and FU) versus oral capecitabine. This will be the largest chemotherapy trial of patients aged 65 years and older on record, with a projected accrual of between 600 and 1,800 patients. In addition, President Clinton's June 2000 executive memorandum directing the Department of Health and Human Services to reimburse, through Medicare, costs issuing from clinical trials, was an explicit attempt by the federal government to increase clinical trial participation of elderly American Medicare beneficiaries. Although efforts like these will likely increase the participation of the elderly on clinical trials, legitimate worries on the part of trialists about the possible interaction of comorbidity and cytotoxic chemotherapy in elderly patients will also likely prevent complete representation of elderly cancer patients on trials. Likewise, increased participation in initial trials will not fully quiet legitimate worries about whether actual implementation in the community will achieve the same rates of success.

With respect to the issue of external validity, we agree that the results cannot strictly be applied to populations other than the one we studied. However, as 96% of Americans aged 65 years and older are recipients of Medicare, we do feel confident that the results can be generalized to the population of elderly Americans with stage III colon cancer. Thus, in the face of limited clinical trial data and an enormous burden of cancer among the elderly, studies such as ours may currently be the best source of information for clinicians facing the challenge of caring for individual elderly patients with cancer, for whom individual risks, benefits, and preferences need to be considered.

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Postoperative Breast Irradiation: New Trials Needed in Older Patients

To the Editor: Fisher et al¹, in their randomized trial of breast-conserving surgery for small node-negative tumors, published in the

October 15 issue of the *Journal of Clinical Oncology*, conclude that ipsilateral breast tumor recurrence (IBTR) occurs with enough frequency to justify considering radiotherapy in all patients. We support this conclusion in general, but feel that sufficient evidence is still lacking in older patients. Within the NSABP B-21 study, in women 70 years of age or older, the IBTR rate was only 1.3% per year in those randomized to tamoxifen alone (based on three recurrences), and this does not exclude women who are tumor estrogen-receptor negative. This is in line with a recent review² that indicates a decline in the risk of recurrence in older patients, managed by breast conserving surgery. The more recent trial by Hughes et al³ of women 70 years of age or older treated by wide excision and tamoxifen shows a very low recurrence (1.3%), albeit with a short follow-up of 28 months. In this trial, only one of the 39 deaths in the trial was the result of breast cancer. The competing risks of cardiac disease caused by aging or adjuvant irradiation⁴ also make it difficult to extrapolate findings from randomized controlled trials on younger patients to an older population. We are overtreating the majority for the benefit of the minority who will profit from the treatment. In older, low-risk patients who may have appreciable comorbidity and for whom the proportion benefiting is small, the potential risks and gains of radiotherapy have to be considered carefully. We therefore feel that the role of radiotherapy in the treatment of this group needs further evidence from large randomized controlled trials to answer these questions.

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In Reply: Our article¹ has provided Kunkler et al² with the opportunity to comment on the use of radiation therapy for the treatment of women aged 70 years or older with breast tumors of 1 cm or less. Although we did conclude that "ipsilateral breast tumor recurrence occurs with enough frequency to justify considering radiotherapy in all patients," this was not meant to imply that all patients should necessarily receive such therapy. Rather, we emphasized the need for making a decision about the use of that modality only in conjunction with consideration of a patient's characteristics, which included age, and the characteristics of her tumor. We provided no prescription either for the universal use of radiation therapy or against its use in all women, including those 70 years of age or older.

The findings from our trial demonstrated that overall, radiation therapy has resulted in a significant (ie, about 60%) reduction in ipsilateral breast tumor recurrence (IBTR). Because we found no evidence to indicate that age had an

influence on this relative benefit, we might expect that there would be about a 60% reduction in the rate of IBTR in study participants aged 70 years and older. However, to estimate in elderly women the absolute benefit from radiation therapy over tamoxifen alone, an accurate baseline rate of IBTR needs to be obtained for this subset of women. We reported the estimated rate of IBTR as 1.3% per year in women aged 70 or older who received only tamoxifen. That figure is a rough estimate because there were only 43 patients in the cohort, so a 95% confidence interval is about 0.4% to 4%. To more accurately estimate the baseline rate (eg, to within 0.2%), it would be necessary to have about 2,300 patients in the tamoxifen group, given the amount of follow-up reported for the NASBP B-21 trial. Thus, as Kunkler et al² have suggested, larger trials than ours would be necessary to obtain knowledge regarding the absolute benefit from radiation therapy in women aged 70 years or older. Nonetheless, the findings from the NASBP B-21 trial do indicate that there is likely to be some benefit in that age group. Thus, this finding cannot be totally ignored when therapy is contemplated.

Finally, it should be noted that even if the annualized rate of IBTR were only 1.3%, this would amount to a 10-year cumulative incidence of about 12.2% in the absence of other competing risks. The annualized rate of mortality for women over the decade from 70 to 79 years of age is about 3% per year. If this mortality rate is applied to women whose annualized rate of IBTR is 1.3%, this would result in a 10-year cumulative incidence of IBTR of about 10.6%. This is not an insubstantial risk, and depending on the individualized preferences of the patient, the use of radiotherapy may or may not be advisable.

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Surrogate Outcomes in Quality-of-Life Research: Where Will We End Up?

To the Editor: We read with great interest the correspondence between Efficace and Bottomley, and Levine and Ganz, about the role of quality of life in clinical research and daily clinical practice.¹⁻³ In 1996, an Outcomes Working Group of the American Society of Clinical Oncology stated that the outcomes of cancer treatment should be distinguished between patient outcomes (survival and health-related quality of life) and cancer outcomes (clinical response) and that the highest priority should be given to patient outcomes.⁴ Despite this recommendation, and despite the fact that the number of trials investigating health-related quality of life has increased in the last 20 years, the ideal integration between clinical research and daily clinical practice is still far from being reached, and the limits of health-related quality of life are often overcome by the use of questionable surrogate instruments. In our recent systematic review of literature about the quality of life in cancer patients treated with chemotherapy,⁵ only 13 out of 89 randomized clinical trials published between 1966 and 2001 reported health-related quality of life as a primary end point, and just 10 out of these 13 trials used a validated instrument to evaluate the quality of life. Although the quality of the study design has improved from the first trials to the most recent ones, the

number of randomized clinical trials having the quality of life as a primary end point remains extremely low. It follows that for the most part, the data about this key topic have a merely descriptive value, and no definitive conclusions can be drawn. However, in the last years, we have observed a questionable trend to replace health-related quality-of-life outcomes with surrogate outcomes, which are undoubtedly easier to be evaluated but are even more undoubtedly misleading and deleterious, as they are not validated and not strictly related to quality of life. Paradigmatic examples in this regard are the clinical benefit in patients with advanced pancreatic cancer during treatment with gemcitabine;⁶ pain control in patients with advanced, hormone-resistant prostatic cancer treated with mitoxantrone and prednisone;⁷ and clinical benefit in patients with stage IV non-small-cell lung cancer treated with gemcitabine.⁸ Such a habit of using surrogate outcomes of quality of life is, in our opinion, particularly worrying, as it favors the Food and Drug Administration's approval of gemcitabine in patients with advanced adenocarcinoma of pancreas and mitoxantrone combined with corticosteroids as initial chemotherapy for patients with pain related to advanced hormone-refractory prostate cancer.⁹ Likewise, the European Medicines Evaluation Agency, despite the high priority given to health-related quality-of-life outcomes, rarely focuses on health-related quality of life in its documents.¹⁰⁻¹¹ Clinical research on health-related quality of life has many unclear and unsolved problems that often make this kind of research difficult and unsatisfactory for clinicians. However, this is not a sufficient justification to use alternative and nonvalidated instruments to overcome these well-known limits. In our opinion, the use (or abuse) of surrogate outcomes can be really dangerous, as it can give us nothing but surrogate responses. The question of Levine and Ganz, "Where do we go from here?"³ is appropriate and extremely exciting, but we should also ask ourselves where we will end up if we continue to use surrogate end points in quality-of-life research and if we continue to be satisfied with surrogate responses to surrogate questions.

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In Reply: In the letter by Tassinari et al,¹ a new and important issue is raised regarding patient outcomes in clinical research and care. Specifically, to what degree should pain or other specific symptoms, sometimes referred to as measures of clinical benefit, substitute for multidimensional assessments of health-related quality of life (QOL)? There is not a clear-cut answer to this question. In some situations, a simple outcome measure such as pain may be all that is needed for the question to be asked, whereas in other, more complex situations, a multidimensional assessment of QOL may be more relevant.

Recently, the National Cancer Institute (NCI) convened a group of experts as part of a Cancer Outcomes Measurement Working Group (COMWG) to review the state of the art in measuring patient outcomes in these settings. As part of that effort, a major book will be forthcoming in 2003, and scientists from this group will be doing Meet-the-Professor sessions at this year's American Society of Clinical Oncology meeting in Chicago, Illinois, in addition to other presentations they have already made at various scientific meetings. Among the issues discussed by COMWG members and representatives of the Food and Drug Administration was the need to incorporate well-designed, hypothesis-driven QOL measurement strategies into treatment trials, rather than adding them on at the end of protocol development. To this end, many of the U.S. and Canadian cooperative trials groups, as well as Pharmaceutical Research and Manufacturers of America, have such studies underway, and we are hopeful that more scientifically valid and robust studies will be published in the future. When we wrote our editorial, it was in anticipation of seeing the results from this new generation of QOL studies. We are very hopeful that the readers of the *Journal of Clinical Oncology* will see higher-quality outcome studies in the future as a result of the efforts of the scientific community of QOL researchers working more closely with clinical trialists.

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Partnering Between Cancer Centers: The American College of Surgeons, National Cancer Institute, American Cancer Society, Centers of Disease Control, American Society of Clinical Oncology, Society of Surgical Oncology, American Society of Therapeutic Radiation and Oncology, and Association of Community Cancer Centers Are Needed to Stimulate Improved Clinical Cancer Care

To the Editor: Dr. Joseph Simone's¹ editorial on cancer centers in the December 1, 2002, issue of the *Journal of Clinical Oncology* was outstanding. I was pleased to note the inclusion of community cancer centers in his discussion, as well as his observation that clinical cancer care needs the same type of concentrated quality effort that has enhanced the quality of clinical cancer research. One way to improve clinical cancer care would be to stimulate community resources through the 1,400+ American College of Surgeons (ACOS)-approved hospital cancer programs, as well as National Cancer Institute (NCI) centers and Community Clinical Oncology Programs (CCOPs). Many community oncologists are already accruing patients to NCI-approved cancer research trials. A combined effort of the NCI and ACOS to partner with the available "grassroots" resources could improve the level of community clinical cancer management from prevention all the way through rehabilitation.

Improving clinical cancer care should be stimulated by raising the standards for accreditation for leading community hospitals by the ACOS. Such accreditation might also lead to NCI recognition of community cancer centers (many of whom already are CCOPs). Such a designation would encourage local funding to evaluate ways to improve clinical cancer care and should accrue more community patients for NCI-approved cancer control and prevention trials.

Evaluation of compliance with the National Cancer Center Network guidelines, which has been started by the comprehensive centers, may eventually lead to a way for research on and treatment of cancers in adults to reach the level of sophistication shown by the pediatric cancer community. Specific new measures to improve care must be integrated with earlier detection and with better management of cancer patients. Poorly educated populations with limited incomes (found in most communities) need to become aware of the importance of healthy lifestyles and appropriate screening with greater access to early cancer care.

A joint meeting of ACOS, the Association of Community Cancer Centers, the American Cancer Society, Society of Surgical Oncology, American Society of Therapeutic Radiation and Oncology, and the staff of the NCI centers could develop a consensus about types of partnerships between NCI, its comprehensive cancer centers, and the ACOS's Commission on Cancer and Community Cancer Centers. This would undoubtedly improve the clinical cancer management and results for most cancer patients in the United States.

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In Reply: Dr. Frelick's comments are welcome and timely. The National Cancer Advisory Board (NCAB) has commissioned a "P30-P50 Working Group" to assess the National Cancer Institute's (NCI's) cancer centers program and its Specialized Programs of Research Excellence (SPOREs), and to offer recommendations for improvement. One of Dr. Andrew von Eschenbach's charges to the Working Group was to offer recommendations

to expand the outreach and community collaboration of cancer centers. The Working Group met for 6 months, completing its report and presenting it to the NCAB on February 11, 2003. It has subsequently been posted on the NCI Web site. In brief, it proposes that incentives be instituted for the establishment of meaningful affiliations between NCI-designated cancer centers and community organizations that have a serious interest in participating in research and in active dissemination of useful scientific and management information. A large majority of cancer patients are treated outside of academic centers. These settings provide an opportunity for expanding participation in research and the use of guidelines, all in the interest of promoting excellence in cancer care.

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Acute Hypokalemic Tetraparesis Induced by Intravenous Methotrexate

To the Editor: We present a case of a 24-year-old patient with osteosarcoma who was treated with high-dose intravenous (IV) methotrexate (MTX) and who showed repeated episodes of acute onset transient tetraparesis without sensory disturbance immediately after MTX, which might be the result of a MTX-induced hypokalemic paralysis. To our knowledge, this kind of toxicity has not been described before.

A 24-year-old male patient presented to our institution with osteoblastic osteosarcoma. Two years earlier, the osteosarcoma was diagnosed at another hospital and treated with surgical resection and chemotherapy consisting of doxorubicin, ifosfamide, cisplatin, and MTX. The patient described a tetraparesis that occurred immediately after MTX and resolved spontaneously after 24 hours. A cranial CT-scan was normal. The tetraparesis could not be explained, but MTX was omitted in further chemotherapies.

When the patient presented to our hospital, he showed progressive pulmonary metastases refractory to chemotherapy. After informed consent, a chemotherapy with IV high-dose MTX was restarted—2 years after the initial exposure to MTX—consisting of 24.7 g (12 g/m^2) MTX in 1,000 mL 5% dextrose + 100 mL sodium bicarbonate over 4 hours with usual antiemetics, hydration, and alkalization of urine. Thirty minutes after the end of MTX infusion, the patient started to develop progressive muscular weakness beginning in both hands. After 6 hours, he showed a tetraparesis, was unable to lift his limbs against resistance, had weakness of the muscles of his neck, was unable to support his head, and had slight difficulty swallowing. There was no disturbance of respiratory musculature, nor was there any sensory loss. After a total duration of 20 hours, the paralysis was gone completely and the patient was left with generalized muscular pain lasting 1 day. On starting the chemotherapy, the serum potassium was in the upper normal range but was 2.8 mmol/L 30 minutes after the end of MTX. Despite immediate supplementation of potassium at a rate of 40 mmol/h IV, the serum level fell to 1.3 mmol/L at 4 hours after the end of MTX. The patient was monitored on an intensive care unit. MTX clearance was normal, as were urinary potassium excretion, urinary pH (> 7.5), serum pH, serum calcium, serum myoglobin, and thyroid function tests. The timing of MTX infusion, potassium supplementation, serum potassium, and muscular weakness are shown in Fig 1.

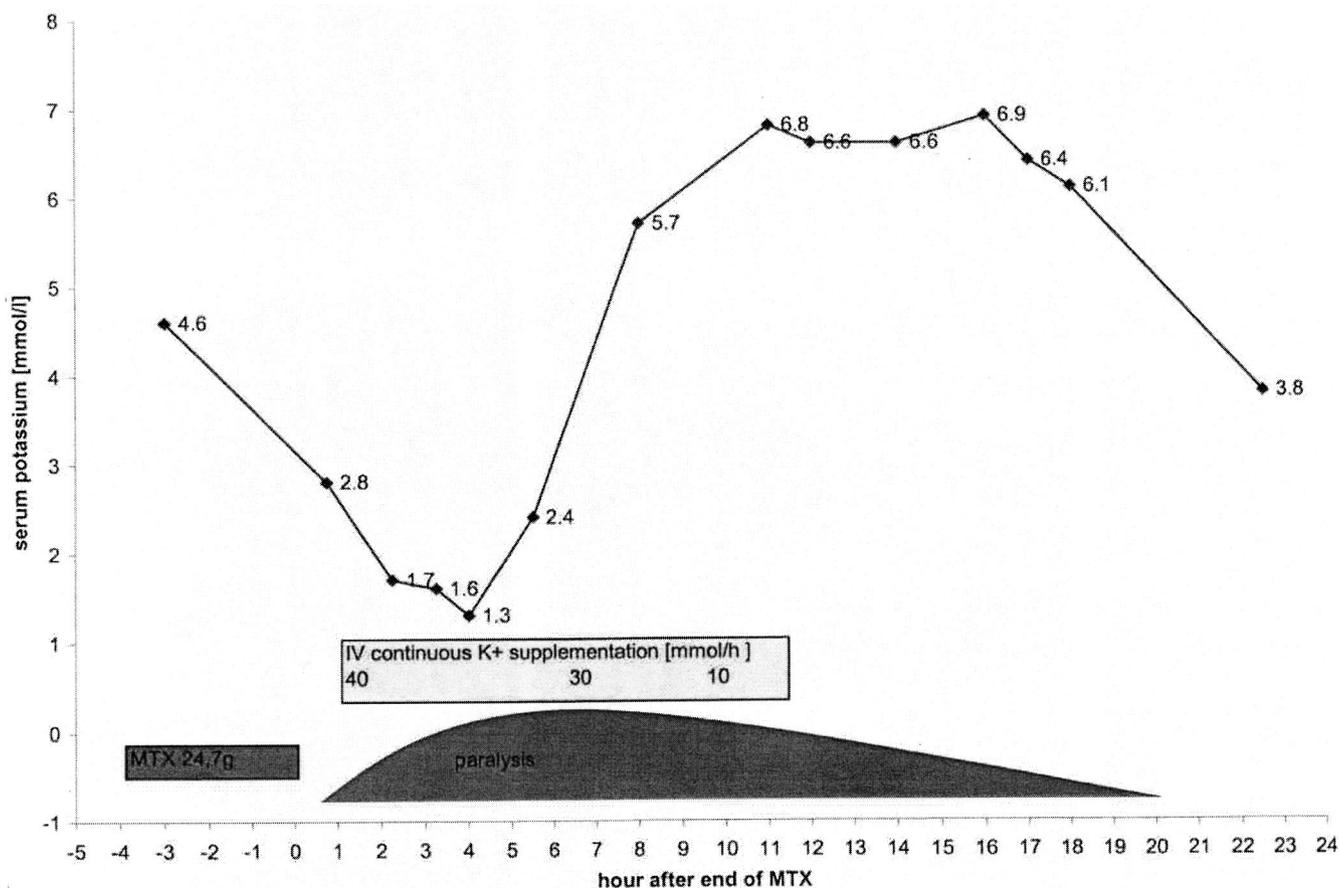


Fig 1. Timing of methotrexate infusion, serum potassium concentration, potassium supplementation, and degree of paralysis.

To exclude bicarbonate as the cause of hypocalcemia or paralysis, after informed consent of the patient, the regimen was repeated using the same protocol for hydration and urine alkalization as before but without MTX. No muscle weakness or changes of serum potassium were noted. At the patient's request, two additional cycles of chemotherapy with high-dose MTX 12 g/m² were administered. With more intensive monitoring of serum potassium and vigorous supplementation, potassium levels fell to a minimum of 2.3 mmol/L in the second cycle and 4.3 mmol/L in the third cycle. Tetraparesis followed the same time schedule as above but was less pronounced in the second cycle and even less so in the third cycle, but was still noticeable. Electromyography performed during an episode of paralysis showed changes consistent with a disturbed electromechanical connection.

Neurological symptoms after intrathecal or systemic chemotherapy with MTX have been described and include reversible acute reactions that appear within 12 hours following MTX, consisting of transient meningism, headache, vomiting, or backpain; reversible subacute reactions occurring days to weeks after therapy with paraparesis, cranial nerve palsies, and cerebellar abnormalities; and late effects with an often irreversible form of leukoencephalopathy presenting with personality disorders and dementia.^{1,2} Cases of unilateral muscle weakness or transient tetraparesis described mainly occur after intrathecal MTX. All cases including one case of transient ascending neuromuscular paralysis³ after IV high-dose MTX occurred at an interval of at least 5 days after MTX. The incidence of neurologic complications after IV high-dose MTX is described as 2.3% to 15%^{2,4} in older case series. Mechanisms of MTX-induced transient neurotoxicity discussed are buildup of toxic intracellular oxidized folates, depletion of tetrahydrobiopterin in the brain via MTX-induced inhibition of dihydrofolate reductase (which is necessary for hydroxylation of biogenic amines), or chemical arachnoiditis.^{2,5,6}

To our knowledge, a muscular paralysis starting immediately after the end of IV MTX has not been described before. It is difficult to explain an immediate onset of paralysis by chemical arachnoiditis or accumulation of intracellular toxins, as acute and subacute neurotoxicity described in the literature usually occur with a time interval after repeated administrations of MTX.¹⁻³ In the case described here, the mechanism by which MTX induced immediate but transient tetraparesis is probably the result of a MTX-induced hypokalemia. Paralysis could be alleviated by potassium supplementation. Hypokalemia cannot be explained by urinary loss, as urinary potassium concentration was within normal limits and urinary volume was not grossly increased. Low serum potassium might be caused by an MTX-induced malfunction of ion channels on the skeletomuscular membranes known as hypokalemic periodic paralysis (hypoPP).⁷ HypoPP usually is a familial disorder caused by inherited typical channelopathies of Na⁺, K⁺, or Ca²⁺ channels. Ion channel malfunction is usually well compensated, so that special exogenous or endogenous triggers are required to produce symptoms. Provoking factors include carbohydrate-rich meals, rest after exercise, sudden exposure to heat or cold, glucose perfusion, and acute stress. By exposing the patient to the hydration, antiemetic, and alkalization regimen omitting MTX, MTX could be identified as the causative drug. MTX as a trigger for a channel malfunction has not been described before.

The patient described here did not have a history of paralysis himself. His mother had epileptiform fits in her puberty, which might possibly point to a

familial disorder, as fits or paralysis can both be presentations of the same channelopathy, depending on the degree of channel malfunction. A search for the most common mutations associated with channelopathies was performed. No mutations were identified in the most frequent loci (R528H, R1239H, and R1239G for the L-type calcium channel and R672H, R672G, and R672S for the sodium channel). However, in case series of HypoPP-patients, 22% of mutations remain undetected.⁸

The presentation of the tetraparesis at the late age of 24 years is atypical for any known mutation causing a channelopathy. At present, a channelopathy as the cause of the paralysis cannot be proven.

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